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TRANSFUSION

CASE REPORT

Thrombocytapheresis for acquired von Willebrand syndrome in a patient with essential thrombocythemia and recent multivisceral transplantation

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Abstract

Background: Essential thrombocythemia (ET) is associated with increased risk of bleeding secondary to acquired von Willebrand syndrome (AVWS). Bleeding in ET requires urgent platelet reduction by cytoreductive therapy such as hydroxyurea or thrombocytapheresis. We report on the efficacy and safety of thrombocytapheresis in managing AVWS in a patient with ET and multivisceral transplantation.

Case report: The patient was a 51-year-old female who underwent multivisceral transplantation. Her postoperative course was complicated by bleeding from oral cavity, IV lines, gastrointestinal and upper respiratory tracts as well as vaginal bleeding, which coincided with ET flare with a platelet count of 1512×10^9/L. Coagulation studies including von Willebrand factor (vWF) antigen and activity, vWF propeptide antigen, and vWF multimer analysis were consistent with AVWS. Hydroxyurea was initiated. However, due to major bleeding, rapidly increasing platelet count, and uncertainty of response to hydroxyurea being given through the enteral tube, thrombocytapheresis was initiated for rapid platelet reduction. The patient tolerated the procedure well. Platelet count was reduced from 1636×10^9/L to 275×10^9/L with rapid cessation of bleeding. The patient's condition stabilized over the next few days; however, bleeding recurred with increasing platelet count, which required a second thrombocytapheresis 8 days after the first one. The patient was maintained on hydroxyurea 500 mg twice/day. At 11-month follow-up, she had a normal platelet count and no recurrence of bleeding.

Discussion: Thrombocytapheresis is safe and efficient in managing postoperative bleeding due to ET/AVWS in solid organ transplant patients. The procedure can be an adjunct to bridging therapy before response to hydroxyurea is achieved.

Previous Presentation: This work was presented, in part, at the American Society for Apheresis Annual Meeting, May 12–15, 2021.

KEYWORDS

acquired von Willebrand syndrome, efficacy, essential thrombocythemia, multivisceral transplantation, safety, thrombocytapheresis

1 | INTRODUCTION

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm that primarily involves the megakaryocytic lineage.[1] It is characterized by sustained increase in platelet count ($\geq 450 \times 10^9$/L) and increased number of mature megakaryocytes in the bone marrow.[1,2] ET is associated with an increased risk of thrombosis and bleeding. Bleeding in patients with ET can be associated with acquired von Willebrand syndrome (AVWS).[3] AVWS is characterized by clinical features and laboratory findings similar to those seen in inherited von Willebrand disease (vWD).[4] Various mechanisms have been implicated in AVWS, with the majority leading to increased clearance or degradation of circulating von Willebrand factor resulting in selective loss of vWF high molecular weight (HMW) multimers.[5]

Bleeding in ET requires urgent platelet reduction by platelet cytoreductive agents such as hydroxyurea or by thrombocytapheresis, which is considered category II indication in managing symptomatic thrombocytosis according to the 2019 American Society for Apheresis (ASFA) guidelines.[5-7] We report on the efficacy and safety of thrombocytapheresis in managing AVWS in a patient with ET and recent multivisceral transplantation. To the best of our knowledge, there are no published reports on thrombocytapheresis in this setting.

2 | CASE PRESENTATION

Our patient was a 51-year-old African American female who recently underwent multivisceral organ transplantation that involved the stomach, small bowel, pancreas, and liver. The patient's medical history was significant for *JAK2*-positive ET, liver cirrhosis secondary to Budd–Chiari syndrome, heparin-induced thrombocytopenia, and multiple thromboses. The patient was maintained on aspirin and coumadin until surgical admission for transplantation. She received bridging parenteral anticoagulation perioperatively with bivalirudin that was held a day before surgery and was restarted 5 days postsurgery. Her postoperative course was complicated by fungal infection and bleeding, requiring exploring laparotomy and partial gastric resection. She subsequently developed bleeding from oral cavity, oozing from IV lines, gastrointestinal and upper respiratory tracts as well as vaginal bleeding, which coincided with ET flare. Complete blood count at the time of bleeding showed WBC of 38,700/uL, hemoglobin value of 7.2 g/dL, and platelet count of 1512×10^9/L. Basic coagulation studies revealed increased activated partial thromboplastin time of 37 sec (22.0–36.0 sec), mildly increased prothrombin time of 14.6 sec (12.1–14.5 sec), normal fibrinogen level of 425 mg/dL (200–450 mg/dL), and increased D dimers of 12.44 ug/ml (<0.51 ug/ml). vWD evaluation during the ET flare showed increased Factor VIII activity of 314% (50–150%), increased von Willebrand factor (vWF) antigen of 317% (50–150%), low vWF activity of 50% (51–215%), very low vWF activity/antigen ratio of 0.16, normal vWF propeptide antigen and absence of HMW multimers on vWF multimer analysis. This profile was consistent with AVWS.

Following this major bleeding event, bivalirudin was discontinued as well as aspirin. Antifibrinolytic therapy with IV tranexamic acid was initiated with modest clinical improvement. Due to previous history of extensive thrombosis and hypercoagulable state, fondaparinux at a prophylactic dose of 2.5 mg was initiated once hemostasis was achieved but was stopped again because of recurrent bleeding. Cytoreductive therapy with hydroxyurea was initiated at a starting dose of 15–20 mg/kg/day and was adjusted with a goal to decrease platelet counts below 450×10^9/L. Due to major bleeding, rapidly increasing platelet count, and uncertainty of response to hydroxyurea being given through the enteral tube, thrombocytapheresis was initiated for rapid reduction of platelets. After obtaining informed consent, thrombocytapheresis was performed using the Spectra Optia (Terumo BCT, Lakewood, CO) processing 2.0 total blood volumes through a temporary femoral central venous catheter. Manufacturer's recommendations were followed to perform therapeutic thrombocytapheresis. Anticoagulant citrate dextrose solution, solution A (ACD-A) was used with an inlet:AC ratio 10:1. A total of 4 g of IV calcium gluconate was infused throughout the procedure. The patient tolerated the procedure well. Platelet count was reduced from 1636×10^9/L to 275×10^9/L with rapid cessation of bleeding. A second thrombocytapheresis was performed 8 days following the first session due to increased platelet count, recurrent gastrointestinal bleeding, and worsening anemia; the procedure was tolerated well, and platelet count was reduced from 1035×10^9/L to 266×10^9/L (Figure 1). The patient was maintained on hydroxyurea

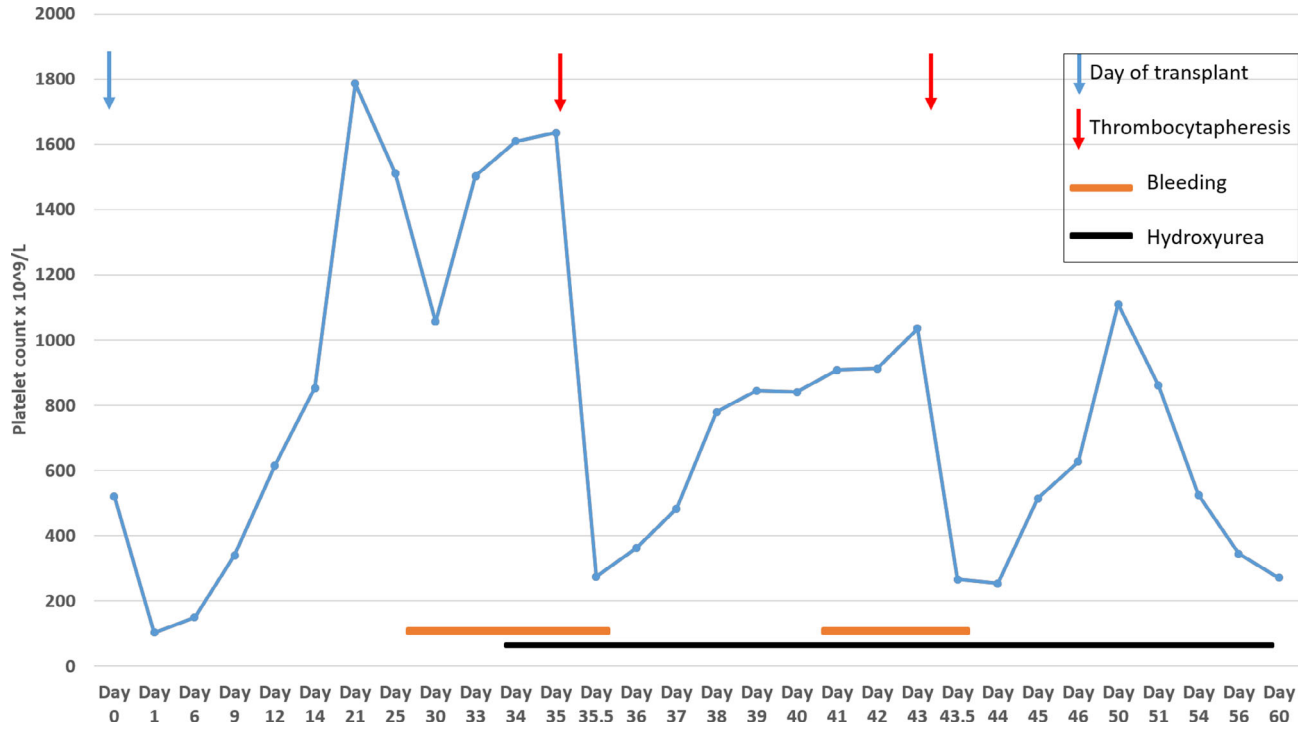

FIGURE 1 Platelet count changes with clinical symptoms and therapeutic course. The horizontal axis represents follow-up time in days from transplant. The vertical scale represents platelet count

500 mg twice a day. She had another transient increase in her platelet count 1 week after the second procedure without evidence of bleeding. At 11-month follow-up, she had a normal platelet count and no recurrence of bleeding.

3 | DISCUSSION

AVWS is defined as any qualitative, structural, or functional disorder of vWF that is not inherited and is often associated with bleeding risk.[8] The pathogenesis of AVWS involves multiple proposed mechanisms including development of antibodies to vWF, increased plasma clearance of vWF by cell adsorption, shear stress, or increased proteolysis.[9, 10] AVWS is recognized in the setting of background disease processes, which include lymphoproliferative, myeloproliferative, cardiovascular, and immunological disorders.[11] Lymphoproliferative disorders account for a substantial percentage of AVWS cases[11]; only few studies have explored the association of myeloproliferative neoplasms with AVWS. In a retrospective study by Mital and colleagues on 170 patients regarding the prevalence of AVWS in patients with ET showed that AVWS was found in 34 (20%) patients indicating that a significant population of ET patients may develop this syndrome.[12] Predictors of AVWS in patients with ET included younger age, higher hemoglobin levels, and the presence of *JAK2V617F* mutation. The group recommended the need to screen patients with ET and signs of bleeding for AVWS, irrespective of the platelet count.[12]

Patients with AVWS demonstrate a bleeding diathesis usually late in life without any past or family history of bleeding. The diagnosis is based on clinical findings and laboratory tests used to diagnose inherited vWD.[13] Samples show a marked decrease in vWF activity with normal or mildly decreased vWF antigen, and absence of HMW vWF multimers similar to type 2A or 2B vWD.[14, 15] Plasma vWF propeptide, which correlates with vWF biosynthesis, will be normal as AVWS is characterized by increased clearance of vWF only.[16]

The aims of treatment in AVWS patients are to rapidly control or prevent acute bleeding and achieve a stable remission of the syndrome. Treatment of the underlying associated condition is the only potential cure for AVWS.[4] Bleeding risk in patients with ET increases significantly when the platelet count is >1000–1500 $\times$ 10^9/L. Rapid control of bleeding can be achieved with different medications including cytoreductive agents, desmopressin (DDAVP), vWF concentrates, or antifibrinolytic agents.[4] Thrombocytapheresis is considered category II indication (i.e., second-line therapy) with Grade 2C recommendation (weak recommendation, low quality or very low quality evidence) in managing symptomatic thrombocytosis according to the 2019 American Society for Apheresis (ASFA) guidelines.[7] It has been

utilized for cytoreduction of patients at increased risk of major bleeding when hydroxyurea is contraindicated or when rapid reduction is necessary.[7, 17, 18]

The paradox of bleeding in a patient with ET and high platelet count is a clinical challenge, and accurate management of AVWS is a matter of clinical judgment among physicians. The suspicion for AVWS was very high in our patient; she had a history of ET without previous personal or family history of bleeding. She manifested with bleeding when her platelet count was above 1000 × 10/L. The diagnosis of AVWS was confirmed with vWD laboratory testing, which revealed a markedly decreased ratio of vWF activity/antigen, absence of HMW vWF multimers, and normal vWF propeptide. Thrombocytapheresis was urgent in our case because of recurrent major bleeding, rapidly increasing platelet count, and the very uncertainty of response to hydroxyurea being given through the enteral tube. Thrombocytapheresis was very efficient in reducing the platelet count, thus achieving rapid cessation of bleeding. A second procedure was performed 8 days after the first session with good tolerance and efficiency. No adverse event was recorded during the two procedures.

4 | CONCLUSION

Thrombocytapheresis is safe and efficient in managing postoperative bleeding due to ET/AVWS in solid organ transplant patients. The procedure can be an adjunct to bridging therapy before response to cytoreductive therapy is achieved.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to transfusion.

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